

ZENECA Pharmaceuticals
A Business Unit of Zeneca Inc.
1800 Concord Pike
P.O. Box 15437
Wilmington, DE 19850-5437

COPY

1
1597 '99 JUN -9 110:50

ZENECA

SENT VIA UNITED PARCEL SERVICE

JUN 7 1999

Dockets Management Branch
HFA-305
Food and Drug Administration
12420 Parklawn Drive
Room 1-23
Rockville, MD 20857

Dear Madam/Sir:

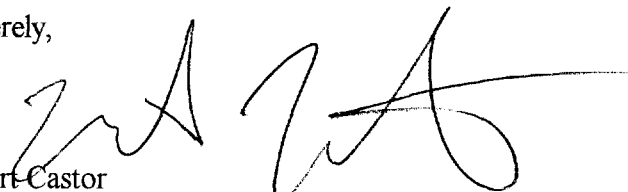
Re: Docket Number 98D-0362

Reference is made to the FDA Draft Guidance for Industry, "Stability Testing of Drug Substances and Drug Products," which was published in the Federal Register in June, 1998.

Zeneca Pharmaceuticals has reviewed this draft document. Our comments on the subject of site-specific stability are attached.

Please do not hesitate to contact me should you require clarification on any of the above comments.

Sincerely,



Robert Castor
Assistant Director
Chemistry, Manufacturing, & Controls Group
Drug Regulatory Affairs Department
(302) 886-2594
(302) 886-2822

RC/CSF/hkd

98D-0362

C62

Site-Specific Stability Comments

The following comments summarize the collective thinking of Zeneca Pharmaceuticals.

Several places in the Draft Stability Guidance contain references to primary stability batches being made at the intended commercial site. Also, references to site-specific data are given in Tables 11 and 12 even in the case where sufficient primary stability data are available for drug substance, simple, or complex dosage forms.

The scientific basis for the need for site-specific stability data is not established. To our knowledge, limited data has been provided to suggest that conducting site-specific stability on drug substances and products, produced on similar equipment, will address safety and efficacy issues.

We believe that rigorous process validation and technology transfer presents a true measure of the potential issues raised by manufacture in alternate sites. Site-specific stability is not the optimal tool for measuring product comparability between two sites.

We disagree with the requirement for site-specific stability for the reasons outlined below: the policy conflicts with The FDA Modernization Act (FDAMA), ICH, and CBER policy; in addition, there are economic, health care, and review concerns.

FDAMA

Our view is that the Draft Stability Guidance, in several areas, outlines requirements for site-specific stability data that is directly contrary to FDAMA and to the amendment of the FD&C Act (Section 505 (c)) on this important subject. The following references clearly support approval of products manufactured at a pilot or small facilities:

- FDAMA Section 608 of the Senate Bill and Section 121 of the House Bill states, “ A drug manufactured **in a pilot or other small facility** may be used to demonstrate the safety and effectiveness of the drug and to obtain approval for the drug prior to manufacture of the drug in a larger facility, unless the Secretary makes a determination that a full scale production facility is necessary to ensure the safety or effectiveness of the drug.”
- Senate Report on Section 608 of S.830 states that , “The legislation therefore states the general rule that the FDA review and approve new drugs and biological products on the **basis of pilot and small-scale manufacturing**, and permit the company to scale up to a larger facility after the product has been approved. Scaling up can readily be undertaken on the basis of **process validation**, without additional clinical trials. Only in the very rare case where full-scale production is necessary to ensure the safety or effectiveness of the new drug or biological product prior to approval is the FDA given the authority to require such manufacture as a condition of approval.”

Zeneca Pharmaceuticals Commentary-Page 2

ICH and other Guidances

The Stability Guidance also appears to indicate that ICH guidances represent minimum site-specific stability requirements. We believe that FDA has, in the past, communicated their intent to view ICH and other guidances as the regulatory ceiling.

The ICH Guidance provides for the submission of data generated in pilot scale facilities and supports the submission of commitment batches at the production site.

Additional support for the notion of submitting data generated at pilot facilities comes from the CBER document, "FDA Guidance Document Concerning Use of Pilot Manufacturing Facilities for the Development and Manufacturing of Biological Products"(July 11, 1995). This guidance announces that **biological products manufactured at pilot or small scale facilities** could be used to demonstrate safety and efficacy for purposes of approval.

Given the above references, we request that **CBER's initiative**, with biological products being approved at pilot or small scale facilities, be extended to **CDER policy with regard to new drug products**.

Economic and Healthcare Issues

A requirement for site-specific data would require large batches of bulk drug to be made very early in the drug development process. In many cases, this will cost millions of dollars for drugs which will be past its retest date before the product is approved.

Capital investments in facilities would be needed to provide for large capacity manufacture of the "new drug" before product efficacy is demonstrated. Alternatively, if the investment is delayed until product efficacy is assured, delivery of the drug product would be substantially delayed to the patient population.

Agency Impact

Site-specific stability represents an additional Agency review requirement.

Proposal

We support the proposal to submit release data from validation lots and the validation summary in lieu of site-specific stability data. This would allow the industry and Agency to comply with FDAMA and ICH, while relieving the economic, healthcare, and review burden associated with site-specific stability.

Zeneca Pharmaceuticals Commentary-Page 2

ICH and other Guidances

The Stability Guidance also appears to indicate that ICH guidances represent minimum site-specific stability requirements. We believe that FDA has, in the past, communicated their intent to view ICH and other guidances as the regulatory ceiling.

The ICH Guidance provides for the submission of data generated in pilot scale facilities and supports the submission of commitment batches at the production site.

Additional support for the notion of submitting data generated at pilot facilities comes from the CBER document, "FDA Guidance Document Concerning Use of Pilot Manufacturing Facilities for the Development and Manufacturing of Biological Products"(July 11, 1995). This guidance announces that **biological products manufactured at pilot or small scale facilities** could be used to demonstrate safety and efficacy for purposes of approval.

Given the above references, we request that **CBER's initiative**, with biological products being approved at pilot or small scale facilities, be extended to **CDER policy with regard to new drug products**.

Economic and Healthcare Issues

A requirement for site-specific data would require large batches of bulk drug to be made very early in the drug development process. In many cases, this will cost millions of dollars for drugs which will be past its retest date before the product is approved.

Capital investments in facilities would be needed to provide for large capacity manufacture of the "new drug" before product efficacy is demonstrated. Alternatively, if the investment is delayed until product efficacy is assured, delivery of the drug product would be substantially delayed to the patient population.

Agency Impact

Site-specific stability represents an additional Agency review requirement.

Proposal

We support the proposal to submit release data from validation lots and the validation summary in lieu of site-specific stability data. This would allow the industry and Agency to comply with FDAMA and ICH, while relieving the economic, healthcare, and review burden associated with site-specific stability.

Site-Specific Stability Comments

The following comments summarize the collective thinking of Zeneca Pharmaceuticals.

Several places in the Draft Stability Guidance contain references to primary stability batches being made at the intended commercial site. Also, references to site-specific data are given in Tables 11 and 12 even in the case where sufficient primary stability data are available for drug substance, simple, or complex dosage forms.

The scientific basis for the need for site-specific stability data is not established. To our knowledge, limited data has been provided to suggest that conducting site-specific stability on drug substances and products, produced on similar equipment, will address safety and efficacy issues.

We believe that rigorous process validation and technology transfer presents a true measure of the potential issues raised by manufacture in alternate sites. Site-specific stability is not the optimal tool for measuring product comparability between two sites.

We disagree with the requirement for site-specific stability for the reasons outlined below: the policy conflicts with The FDA Modernization Act (FDAMA), ICH, and CBER policy; in addition, there are economic, health care, and review concerns.

FDAMA

Our view is that the Draft Stability Guidance, in several areas, outlines requirements for site-specific stability data that is directly contrary to FDAMA and to the amendment of the FD&C Act (Section 505 (c)) on this important subject. The following references clearly support approval of products manufactured at a pilot or small facilities:

- FDAMA Section 608 of the Senate Bill and Section 121 of the House Bill states, “ A drug manufactured **in a pilot or other small facility** may be used to demonstrate the safety and effectiveness of the drug and to obtain approval for the drug prior to manufacture of the drug in a larger facility, unless the Secretary makes a determination that a full scale production facility is necessary to ensure the safety or effectiveness of the drug.”
- Senate Report on Section 608 of S.830 states that , “The legislation therefore states the general rule that the FDA review and approve new drugs and biological products on the **basis of pilot and small-scale manufacturing**, and permit the company to scale up to a larger facility after the product has been approved. Scaling up can readily be undertaken on the basis of **process validation**, without additional clinical trials. Only in the very rare case where full-scale production is necessary to ensure the safety or effectiveness of the new drug or biological product prior to approval is the FDA given the authority to require such manufacture as a condition of approval.”

ICALS

1 LBS 1 OF 1

5630
1 fl

DOCKETS MANAGEMENT BRANCH
20 PARKLAWN DR
ROCKVILLE MD 20857

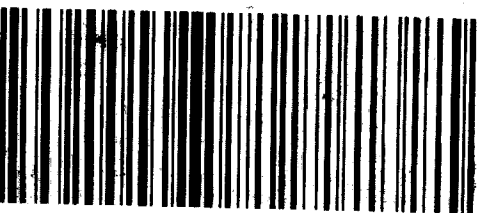
(420) SHIP TO POSTAL CODE



(420) 20857-0000

OUND

#:1Z X29 W25 03 0005 3361



PBAM3.0

Dockets Management Branch

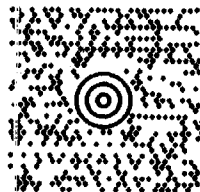
HFA - 305

Food and Drug Administration

12420 Parklawn Drive

Room 1-23

Rockville, MD 20857



SHIP DOCKETS CONTROL CLERK
TO: ROOM 1630
5630 FISHERS LANE
ROCKVILLE MD 20852

